When features of prior art references are combined to establish obviousness, the mere possibility of such a combination does not render the result of that combination obvious absent a logical reason of record which justifies the combination. In re Regel, 526 F.2d 1399, 188 USPQ 136 (CCPA 1975). Instead, references may only be modified when (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or perform the claimed process, and (2) that those of ordinary skill in the art would have a reasonable expectation of success of making the claimed composition or performing the claimed process. "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not the applicant's disclosure." In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Further, the rejection cannot be predicated on the mere identification of individual components in the prior art. "Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for the combination in the manner claimed." In re Kotzab, 217 F.3d 1365, 1371 (Fed. Cir. 2000).

Thus, there must be a reason apparent to one skilled in the art at the time of the invention for applying the teaching at hand, or the use of the teaching as evidence of obviousness entails prohibited hindsight. Graham v. John Deere Co., 383 US 1, 148 USPQ 459 (1966); In re Dembiczak, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

Based on the foregoing case law, and according to MPEP 2143, three basic criteria must be met to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure, as such would be indicative of impermissible hindsight.

Thus, to establish a *prima facie* case of obviousness, the Examiner is required to cite a combination of prior art that not only teaches each and every element of the rejected claims, but also is required to cite substantial evidence to support the conclusion that one of ordinary skill in the art would be motivated to combine or modify the references as suggested, as well as

substantial evidence that one of ordinary skill in the art would have a reasonable expectation of success in making the cited combination or modification.

It is respectfully submitted that the Examiner has not met the initial burden of setting forth a *prima facie* case of obviousness. First, it is duly noted that, in order to establish a *prima facie* case of obviousness, the Examiner must establish that the prior art provides some teaching, suggestion or motivation to combine or modify the cited references. Further, the Examiner must show that one of ordinary skill in the art would have a reasonable expectation of success in making the claimed invention. Finally, the Examiner is required to support the obviousness rejection with actual evidence, as opposed to mere conclusory statements. See In re Zurko, 142 F.3d. 1447, 46 USPQ2d 1691 (Fed. Cir. 1998).

The Prior Art Teaches Away From the Invention of Applicant's Claim 1

The characteristic tendency to form a gelatinous mass in contact with water is unique to cefuroxime axetil. Therefore, in formulating a solid format of cefuroxime axetil, one must not only provide a barrier layer to protect against bitterness, but must also make sure that the barrier layer does not induce gel formation by rupturing too slowly.

For example, Deutsch *et al.* teaches that a coated tablet of cefuroxime axetil must combine two critical components to prevent gel formation: i) a thin film-coating with a **rupture time of less than 40 seconds**; and ii) an effective amount of disintegrant to produce tablet core disintegration immediately following film coat rupture. Indeed, the prior art as a whole (including Deutsch *et al.*) teaches that the rupture time must be less than 40 seconds or gelling occurs, inhibiting bioavailability.

Deutsch *et al.* teaches a formulation of cefuroxime axetil with a film coating having a rupture time of **less than forty seconds**. Deutsch *et al.* does not disclose or teach any solid oral format of cefuroxime axetil that does not gel when the protective taste masking barrier layer has a rupture time greater than 40 seconds. Indeed, an important teaching of Deutsch *et al.* is that the film coating must rupture in **less than forty seconds** for the formulation to be effective, because the prior art teaches that a longer rupture time leads to gel formation and poor disintegration and hence dissolution of the antibiotic. Thus, the prior art teaches that the rupture time cannot exceed forty seconds, and therefore, the prior art as a whole teaches away from the invention of Applicant's claim 1.

Furthermore, there is no teaching in the prior art of record that one of ordinary skill in the art would be motivated to modify the cited references, or would have a reasonable expectation of success in modifying Khan *et al.*, as suggested by the Examiner. Based on the teachings of Deutsch *et al.*, which clearly requires that the barrier film layer for taste masking of a cefuroxime tablet must rupture in less than 40 seconds, even if the core tablet contains high levels of disintegrant, to prevent gel formation which impairs dissolution, person of ordinary skill in the art would not be motivated to modify the tablet of Khan *et al.* and use a capsule as a barrier film layer for taste masking, considering that commercially available capsules are known to have long rupture times significantly in excess of 40 seconds.

More particularly, there is no teaching in the prior art of record that one of ordinary skill in the art would be motivated to modify Khan *et al.*, or would have a reasonable expectation of success in modifying Khan *et al.*, as suggested by the Examiner. Khan *et al.* clearly requires a double layered film-coat for the cefuroxime axetil tablet of his invention to rupture in more than 40 seconds without gelling of the cefuroxime axetil. Not just any double layered film-coat will work in Khan's invention, and Khan *et al.* specifically discloses the different compositions of the double layered film-coat of his invention. It would not have been obvious for a person ordinarily skilled in the art based on Khan's teaching, to try to use a single-layered capsule (of a homogeneous composition).

Amey *et al.* also does not cure the deficiencies of Khan *et al.*, rather Amey *et al.* merely teaches a process for encapsulation of caplets in a capsule by cold-shrinking. The objective of Amey *et al.* is to provide a tamper-proof solid format: "The solid dosage form according to the present invention is tamper-proof in that the caplet contained in the capsule cannot be removed from the capsule without destroying same (capsule)" (column 2, lines 19-22).

In the same way that a person of ordinary skill in the art would not take the teaching of Khan *et al.* and use a single-layered capsule (of a homogeneous composition) which has a long rupture time as barrier layer for a cefuroxime axetil tablet, a person of ordinary skill in the art would not also take the teaching of Amey *et al.* on a process for cold-shrinking capsule onto a caplet for tamper-resistance and use a cold-shrunk capsule to prevent gel formation of a solid format of cefuroxime axetil. In fact, the tablet-in-a-capsule embodiments of Applicant's invention use commercial capsules without cold-shrinking, and are not tamper resistant because the tablet can be removed readily from the capsule without destroying the capsule. Amey *et al.*

does not disclose or teach any solid oral format of cefuroxime axetil that i) is not cold-shrunk; and ii) does not gel when the protective taste masking barrier layer has a rupture time greater than 40 seconds. In short, there is nothing in the prior art that would have motivated one of ordinary skill to combine Khan *et al.* and Amey *et al.* as suggested by the Examiner, because there would have been no reasonable expectation of success, particularly since Khan *et al.* clearly specifies a double layered film-coat of specific composition to prevent gel formation.

Applicant's Have Shown Unexpected Results

Applicant's invention provides a core tablet containing the antibiotic cefuroxime axetil inside a capsule, which serves to mask the bitter taste of the drug. Applicant has unexpectedly found that, in contrast to the teachings of the prior art pertaining to the film-coated tablet of cefuroxime axetil (*i.e.*, Deutsch *et al.*), Applicant's tablet-in-a-capsule format does not result in gel formation of cefuroxime axetil, even if the rupture time of the taste masking barrier (capsule) is significantly longer than the forty (40) second time limit for the film-coated tablet of cefuroxime axetil. The longer rupture time of Applicant's tablet-in-a-capsule improves taste masking without sacrificing dissolution of cefuroxime axetil. However, the prior art teaches that the rupture time cannot exceed forty seconds, and therefore the prior art teaches away from the claimed invention.

Despite the actual very long *in vivo* disintegration time, Applicant's invention is bioequivalent to the commercial product based on the patent to Deutsch *et al.* (Glaxo's Ceftin, see Example 4 of Applicant's patent application). Clearly, from the teachings of the prior art, a person of ordinary skill in the art would not consider using commercial capsules as barrier layers for cefuroxime axetil, because their rupture time is significantly longer than 40 seconds, a rupture time for film coating that Deutsch *et al.* teaches to cause gel formation of the core cefuroxime axetil tablet. Moreover, a person of ordinary skill in the art would not be motivated to put a core antibiotic tablet inside a capsule, because it is easier to simply fill the antibiotic as granules, without tabletting, into the capsule. Indeed, Applicant is aware of no commercial antibiotic that is sold anywhere in the world as a tablet-in-a-capsule.

Furthermore, if a capsule is the desired format, a person of ordinary skill in the art would simply take antibiotic granules, without tabletting, to fill directly into capsules for taste masking. It is highly unusual and therefore non-obvious to take the extra steps of tabletting the antibiotic

and then filling the tablet into capsule (a difficult operation commercially), if the objective is simply taste masking. However, as shown in the examples of the present application, filling cefuroxime axetil granules directly into capsules, even with high levels of disintegrant, still results in gel formation and hence poor dissolution.

As the examples in Applicant's patent application show, cefuroxime axetil filled as granules into capsules, as a person of ordinary skill in the art would do for antibiotic capsules, results in gel formation of the cefuroxime axetil and hence poor dissolution. However, Applicant has unexpectedly discovered that, by tabletting the same formulation of cefuroxime axetil granules and filling into capsules as tablets, gel formation does not occur, even if the mean rupture time (as in our examples) is about 180 seconds. These unexpected results of Applicant's experiments are not taught or suggested by the prior art, indeed, the prior art of record teaches away from Applicant's results.

The present invention provides a core tablet containing the antibiotic cefuroxime axetil inside a capsule, which serves to mask the bitter taste of the drug. Applicants have found surprisingly that, in contrast to disclosures of the prior art pertaining to film-coated tablets of cefuroxime axetil, the present tablet-in-a-capsule format does not result in gel formation of cefuroxime axetil, even if the rupture time of the taste-masking barrier (capsule) is significantly longer than the 40 seconds limit for film-coated tablets of cefuroxime axetil. The longer rupture time of the tablet-in-a-capsule improves taste masking, without sacrificing the dissolution of cefuroxime axetil and bioavailability.

The Combination of Khan *et al.* and Amey *et al.*
Does Not Teach or Suggest Each And Every Element of Applicant's Claim 1

The Examiner maintains that Khan *et al.* teaches providing an oral pharmaceutical form of cefuroxime axetil, where the drug is contained in a tablet core and is coated with" a **double layered** film coat" (emphasis added). The first coat masks the bitter taste of the drug and the second coat delays the rupture time beyond 40 seconds. The Examiner acknowledges that Khan *et al.* does not teach a rupture time of more than sixty seconds, as recited in Applicant's claim 1. Nevertheless, the Examiner asserts that a person of ordinary skill in the art at the time of the invention would have been motivated to vary and/or optimize the rupture time to arrive at Applicant's invention.

The Examiner states that: "Khan *et al.* teaches an oral pharmaceutical form of cefuroxime axetil where the drug is contained in a tablet core and is coated with a double layered film coat (see abstract in particular). Khan *et al.* teaches that the first film coat masks the bitter test of the cefuroxime axetil while the second film coat delays the rupture time beyond 40 seconds (see abstract, in particular), and even teaches that the rupture time can be between 45-240 seconds (see page 4, second full paragraph, in particular). Khan *et al.* teaches that the delayed rupture time is desirable because patients find it easier to swallow dosage forms that have a longer rupture time (see paragraph bridging pages 3-4, in particular)."

By seeking to patent a cefuroxime axetil tablet with a novel double layered film-coat to extend rupture time beyond 40 seconds, Khan *et al.* clearly acknowledge the limitation associated with conventional film-coatings known in the art. In particular, page 2 lines 22-27 of WO 02/43707 states: "further, with the relatively slow penetration of moisture, from the film coat to the core, which occurs upon administration of tablets of cefuroxime axetil provided with conventional coats, the cefuroxime axetil present in the tablet core may gel. This gel formation leads to poor dissolution of cefuroxime axetil; thus the absorption from the gastro-intestinal tract is greatly reduced."

Khan *et al.* therefore seeks to patent a new double layered film-coat for cefuroxime axetil tablet that has a rupture time in excess of 40 seconds, without affecting the bioavailability of cefuroxime axetil. Khan *et al.*, however, did not show any bioavailability data, but rather merely showed tablet disintegration. Nonetheless, Khan *et al.* found a novel way to prevent cefuroxime tablet from gelling, even if the rupture time is more than 40 seconds. Although Khan *et al.* showed one way (by using a double layered film-coat) of extending the rupture time beyond 40 seconds without causing tablet gelling, Khan *et al.* did not show that the tablet-in-capsule of Applicant's instant invention would also work. Specifically, the capsules used in the tablet-in-capsule of the instant invention are conventional capsules, which are made up of a single homogeneous layer. Applicants are not aware of any commercial conventional capsule made up of two different layers of materials. Khan *et al.* therefore does not disclose or teach any solid oral format of cefuroxime axetil with a single barrier layer which will not gel, when the protective barrier layer has a rupture time greater than 40 seconds.

The Examiner also acknowledges that Khan *et al.* does not teach providing the tablet in a capsule, or the composition of the capsule. However, the Examiner asserts that Amey *et al.*

teaches a process for encapsulation of caplets in a capsule, and therefore concludes that a person of ordinary skill in the art at the time of the invention would have been motivated to provide the cefuroxime axetil tablet of Khan *et al.* in the capsule of Amey *et al.*, with the expectation of providing a suitable dosage form having a neutral, non-bitter taste, as well as other benefits.

Amey *et al.* discloses a process for encapsulation of caplets in a capsule by cold-shrinking. The objective of Amey *et al.* is to provide a tamper-proof solid format: "The solid dosage form according to the present invention is tamper-proof in that the caplet contained in the capsule cannot be removed from the capsule without destroying same (capsule)" (column 2, lines 19-22). Amey *et al.* further discloses: "According to a specifically preferred embodiment of the present invention, the clearance of the capsule shell and the caplet is in the range of from about 0 to about -0.5mm, which means that the caplet is compressed in the capsule" (column 2, lines 50-54).

The cefuroxime axetil tablet-in-a-capsule format of the invention does not involve cold-shrinking of the capsule onto the caplet (compressed caplet; where compressed caplet as used by Amey *et al.* refers to a caplet compressed by the encapsulating capsule) to provide a tamper-proof caplet. On the contrary, as Applicant's examples clearly show, the cefuroxime axetil tablets are filled into commercially available capsules not intended for cold-shrinking. The cefuroxime axetil tablet of the tablet-in-a-capsule format of the instant invention is not a compressed caplet as defined by Amey *et al.* As disclosed in all Applicant's examples, the cefuroxime axetil tablets are filled into the capsules freely (compare sizes of capsules and tablets in our examples), *i.e.* without force, and therefore can be removed without destroying the capsules.

Applicant therefore believes that the Examiner is using impermissible hindsight in her analysis, in the same vein as the CAFC comments on "hindsight." The only motivation for any combination of the cited references is found in Applicant's application. The combination suggested by the Examiner is made without any reasonable teaching or motivation in the prior art, and moreover does not produce Applicant's invention in any case. That is, there is no teaching or suggestion in the prior art to combine the cited references, and even making the combination suggested by the Examiner does not produce all of the claimed features recited in Applicant's claim 1. Indeed, the prior art teaches away from such a combination.

It is respectfully submitted that the rejection of Applicant's independent claim 1 as being obvious over Khan *et al.* (WO 02/43707) in view of Amey *et al.* is thus overcome. Reconsideration and withdrawal of the obviousness rejection of claim 1 are therefore respectfully requested.

Claims 2-12 and 15-16, being dependent upon and further limiting independent claim 1, should be allowable for that reason, as well as for the additional limitations recited therein. It is respectfully submitted that the rejection of claims 1-12 and 15-16 as being obvious over Khan *et al.* (WO 02/43707) in view of Amey *et al.* is thus overcome. Reconsideration and withdrawal of the obviousness rejection of claims 1-12 and 15-16 are therefore respectfully requested.

Claims 13-14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Khan *et al.* (WO 02/43707) in view of Amey *et al.* (U.S. Pat. No. 6,080,426), and further in view of Xiping Wang (U.S. Pat. No. 6,482,432).

Wang also does not cure the deficiencies of Deutsch *et al.* and Amey *et al.*, rather Wang merely teaches vegetable based capsules. Wang does not disclose or teach any solid oral format of cefuroxime axetil which does not gel when the protective taste masking barrier layer has a rupture time greater than 40 seconds. Therefore, it is respectfully submitted that Applicant's claims cannot be obvious over Wang standing alone or in combination with Khan *et al.* and/or Amey *et al.*

Furthermore, claims 13-14, being dependent upon and further limiting independent claim 1, should be allowable for that reason, as well as for the additional limitations recited therein. It is respectfully submitted that the rejection of claims 13-14 as being obvious over Khan *et al.* in view of Amey *et al.* and further in view of Xiping Wang is thus overcome. Reconsideration and withdrawal of the obviousness rejection of claims 13-14 are therefore respectfully requested.

Conclusion

Based upon the above remarks and the papers of record, Applicant believes that the pending claims of the above-captioned application are in allowable form and patentable over the prior art of record. Applicant therefore respectfully requests reconsideration of the pending claims 1-16 and a prompt Notice of Allowance thereon.

Respectfully submitted,

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